



PATENT
BERTEK 3.0-025

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	:	
Govil et al.	:	
	:	Group Art Unit: 1617
Application No. 08/883,075	:	
	:	Examiner: E. Webman
Filed: June 26, 1997	:	
	:	Date: October 15, 2002
For: ADHESIVE MIXTURE FOR	:	
TRANSDERMAL DELIVERY OF	:	
HIGHLY PLASTICIZING DRUGS	:	
	:	
	X	

Assistant Commissioner for Patents
Washington, D.C. 20231

SUPPLEMENTAL DECLARATION UNDER 37 C.F.R. § 1.131

Sir:

1. I, Dr. Ludwig J. Weimann, am one of the co-inventors with Dr. Sharad K. Govil of the above-identified pending U.S. patent Application No. 08/883,075, filed in the United States Patent and Trademark Office on June 26, 1997.

2. I am presently a consultant for Mylan Technologies, Inc., the assignee of Application No. 08/883,075, but I was employed by Mylan Technologies, Inc. and its predecessor, Bertek, Inc., for about 20 years, and was Senior Director of Research when I retired in 1998.

3. I invented the subject matter of Application No. 08/883,075, including that of claims 84 and 92 therein, with Dr. Govil, and in accordance with our invention we reduced the invention to practice prior to June 7, 1995.

4. I am familiar with the prosecution of this patent application, including the official action dated July 23, 2002. In particular, this official action includes a rejection based upon Mantelle et al., U.S. Patent No. 6,316,022 ("the '022 patent").

5. It is my understanding that the '022 patent has been applied as a reference against Application No. 08/883,075 under 35 U.S.C. § 102(e), based upon a U.S. filing date of June 7, 1995.

6. Dr. Govil and I completed the invention of claims 84 and 92 of our pending application in the United States before the filing date of the '022 patent; namely, before June 7, 1995, claims 84 and 92 reading as follows:

84. A transdermal delivery system consisting essentially of a blend of:

(a) one or more hydrophobic acrylic-based polymers; and

(b) a therapeutically effective amount of one or more drugs, at least one of which is of low molecular weight and liquid at or about room temperatures,

wherein said system is substantially free of water and liquids having a normal boiling point (i) below processing temperatures and (ii) equal to or greater than the normal boiling points of the low molecular weight drugs.

92. A transdermal delivery system consisting essentially of a blend of:

(a) an acrylic-based polymer; and

(b) a therapeutically effective amount of a drug having a low molecular weight and being a liquid at or about room temperatures, wherein said system is substantially free of solvents selected from the group consisting of water and liquids having a normal boiling point

(i) below processing temperature and

(ii) equal to or greater than the normal boiling points of the low molecular weight drugs,

whereby said transdermal drug delivery system, subsequent to processing, is free of said solvents.

7. In particular, prior to June 7, 1995, we were involved in the preparation of a transdermal drug delivery system for use in connection with certain drugs having a low molecular weight, such as selegiline, and their application in a system which could be adhesively applied to the skin.

8. Prior to June 7, 1995, we thus invented and actually reduced to practice a transdermal delivery system for selegiline which used selegiline in a transdermal patch using a non-aqueous solvent in connection with an acrylic adhesive polymer system and employing only solvents which were highly volatile, such as ethanol, which were removed during drying, but we excluded solvents that remained after drying, such as propylene glycol and the like.

We thus employed the low molecular weight drug selegiline, which is a liquid at or about room temperature, along with a polymer system in which the entire system was substantially free of water, as well as liquids which had a normal boiling point below processing temperatures for the patch, and equal to or greater than the normal boiling point of the selegiline.

9. Prior to June 7, 1995, under my direct supervision and control, such selegiline patches were prepared. In particular, as shown on page 77 of Notebook No. 24 (a copy of which is attached hereto as Exhibit A, with the actual dates blanked out), Susan Honn, a laboratory chemist and myself prepared a patch identified as SEL-77C employing 30 mg selegiline, in the free base form, in a 10 cm² patch. In the three patches shown on page 77, the patches included varying percentages of the acrylic pressure-sensitive adhesive known as GELVA 1753 (Monsanto), including 32% solid content and self-cross-linkable acrylic adhesive containing a hardening monomer comprising methyl acrylate along with ethyl acetate in the amounts shown. In particular, the acrylate adhesive GELVA 1753 was mixed with the ethyl acetate and the selegiline drug was added while mixing in order to create a homogeneous blend. A thin film of the drug/adhesive blend was then produced and applied to a release-coated plastic/paper substrate. The coating was then dried in an oven and then laminated to a backing material made of PET/PE and die-cut into patches.

10. All of the patches produced in the manner shown in Exhibit A were free of water and liquids with a normal boiling point below the processing temperature and equal to or greater than the normal boiling points of the drug utilized, and were specifically free of 1,2-propanediol as shown thereon.

11. At a subsequent date, but still prior to June 7, 1995, additional patches were prepared again using selegiline in the free base form, and in this case with and without 1,2-propanediol. These were again prepared by Susan Honn, under my direct supervision and control, and by myself. As is thus shown on pages 143 and 144 of Notebook No. 24 (copies of which are attached hereto as Exhibit B, with the dates blanked out), Examples 2 and 3

included the same GELVA 1753 (Monsanto) previously used, in combination with selegiline in free base form and ethanol. As shown in Example 3 on page 144, 1,2-propanediol was not employed, while in Example 4 it was employed. In the case of Example 3 the selegiline in the free base form was mixed with the ethanol and then added to the adhesive GELVA 1753 while mixing. In Example 4 the ethanol was added to the GELVA 1753 and the selegiline was then mixed with the 1,2-propanediol and added to the GELVA 1753 while mixing.

12. In addition, as shown on pages 152 of Notebook No. 24 (a copy of which is attached here to as Exhibit C with the dates blanked out), Robert Campbell, a lab technician, and myself conducted shear and peel tests, including those for Examples 3 and 4 from page 144. Susan Honn and myself then also calculated the coat weight for these formulations, and these are shown on page 153 of Notebook No. 24 (a copy of which is attached hereto as Exhibit D with the actual dates blanked out), including those from Examples 3 and 4 from page 144.

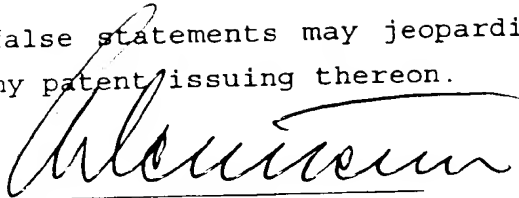
13. Again in each of these cases, all of which were actually carried out prior to June 7, 1995, transdermal patches were produced in which the drug delivery system included a pressure-sensitive adhesive comprising an acrylic polymer (one or more polymers) as well as selegiline in the free base form (a therapeutically effective amount of a drug which is a low molecular weight and a liquid at or about room temperatures) and in which systems were substantially free of water as well as liquids with a normal boiling point below the processing temperature for the patch and equal to or greater than the normal boiling points of the selegiline. These patches were actually produced and tested on dates prior to December 19, 1996.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United

Application No. 08/883,075

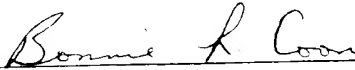
States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

10/25/02
Date


LUDWIG J. WEIMANN

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2-10-03
Expires


Notary

TITLE

Formulation of Selegiline free base Book No. 24

 From Page No. _____ patches with 30mg Selegiline / 10cm² patch

SEL-77A

GMS 1430 (41% solid)

 per solids
70
per liquids
170.7

%

(1/2)

34.2 25.45

1.2 PD

Selegiline free base

30

30.0

3.0

6.0

4.5

Ethyl Acetate

30

30.0

3.0

6.0

4.5

1 step GMS 1430 mix with Ethyl Acetate

2 step Add Selegiline while mixing

SEL-77B

80-1194 (47% solid)

 70.0
149.0

per liquids

(1/2)

29.8

22.35

1.2 PD

Selegiline free base

30

30

6.0

4.5

Ethyl Acetate

30

30

6.0

4.5

SEL-77C

Gelva 1753 (32%)

70.0

219

(1/2)

43.8

32.85

1.2 PD

Selegiline free base

30

30

6.0

4.5

Ethyl Acetate

30

30

6.0

4.5

To Page No. _____

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Date

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Form Page No. _____

Formulations of patcheswith Nefegiline free basewith and without 1.2 Propanediol

#1

1430/26⁰ 1.2 PD
38 + 2 PD / 15 Sel

without 1.2 PD

	solids	liq	1/3 liq
GMS 1430 (41%)	85.0	207.3	69.1
1.2 PD	26.0 0.0	0.0	0.0
Sel free base	15.0 15.0	15.0	5.0
Et OH	30.0 <i>lv</i>	30.0 <i>lv</i>	10.0 <i>lv</i>

#2

1430/35 1.2 PD / 15 Sel

with 1.2 PD

	solids	liq	1/3 liq
GMS 1430 (41%)	50.0	121.95	40.7
1.2 PD	35.0	35.0	11.7
Sel (free base)	15.0	15.0	5.0
Et OH	20.0	20.0	7.0

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 2nd
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 EtOH

Project No. _____

Book No. 24

TITLE

Formulation (cont)

TITLE

Pe.

From Page No. _____

#3

1753 / ~~1.2 PD~~ / 15 Sel without 1.2 PD

	solids	liqu.	$\frac{1}{3}$ liqu.
Gelva 1753 (28.3%)	85.0	303.6	101.2
1.2 PD	0.0	0.0	0.0
Del (free base)	15.0	15.0	5.0
EtOH	30.0 _{lv}	30.0 _{lv}	10.0 _{lv}

Del was mixed with EtOH and added to 1753 while mixing.

#4

1753 / 35 1.2 PD / 15 Sel

	solids	liqu.	$\frac{1}{3}$ liqu.
Gelva 1753 / 35 1.2 PD / 15 Sel			
Gelva 1753	50.0	171.5 176.75	57.17 58.94
1.2 PD	35.0	35.0	11.7
Del (free base)	15.0	15.0	5.0
EtOH	20.0	20.0	7.0

EtOH was added to 1753

Del was mixed with 1.2 PD and added to 1753 while mixing

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Date

Invented by

Date

Recorded by

Witnessed & U

Liz Cox

Project No. _____

Book No. 24TITLE Shear test & peel Test

From Page No. _____

Sample	Adhesive weight mg/10cm ²	Shear (min)	90° peel from s/s g/in	Peel from skin (after 10 min dwell)
#1 pg 143	109.0 144	105.2	1100	clean peel
#2 pg 143	125.2 133	8.8	cohesive failure	transfer to skin
#3 pg 144	125.0 130	1362.4	650	clean peel
#4 pg 144	125.6 126	11.4	cohesive failure	clean peel
#5 pg 147	122.2 144	5.2	600g	transfer to skin
#6 pg 147	122.6 144 w div	104.1	600g	clean peel.

Legend:

- #1 1430 / 0 PD / 15 Sel
- #2 1430 / 35 PD / 15 Sel
- #3 1753 / 0 PD / 15 Sel
- #4 1753 / 35 PD / 15 Sel
- #5 1430 / 26 PD / 11.3 Sel
- #6 1753 / 26 PD / 11.3 Sel

To Page No. _____

Witnessed & Understood by me.

Date

Invented by

Date

Recorded by

Robert Campbell

TITLE Co
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From Page N

#
P143
1
2
P143
2
2
P144
3
3
3
P144
4
4
4
P147
5
15
5
P147
6
6
6
* 1.0 m

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From Page No. 1

#	Formulation	Coat weight plus 1 mil PET	* 0.0315g P69 - 1 mil PET	COAT WEIGHT / 10 CM ²
P143	1430 / 1.2 PD / 15 Sel FB	0.13925	0.1077	$\bar{x} = 113.6 \text{ MG} \pm 6.27 (5.5\%)$
	" " "	0.1517	0.1202	
	" " "	0.1445	0.1130	
P143	1430 / 1.2 PD / 15 Sel FB	0.1647	0.1332	$\bar{x} = 133.17 \text{ MG} \pm 0.75 (0.56\%)$
	" " "	0.1639	0.1324	
	" " "	0.1654	0.1339	
P144	1753 / 15 Sel FB	0.1612	0.1297	$\bar{x} = 129.97 \text{ MG} \pm 0.38 (0.29\%)$
	" " "	0.1613	0.1298	
	" " "	0.1619	0.1304	
P144	1753 / 1.2 PD / 15 Sel FB	0.1863	0.1548	$\bar{x} = 156.13 \text{ MG} \pm 1.89 (1.2\%)$
	" " "	0.1898	0.1583	
	" " "	0.1868	0.1553	
P147	1430 / 1.2 PD / 11.3 Sel FB	0.1833	0.1518	$\bar{x} = 148.97 \text{ MG} \pm 4.23 (2.8\%)$
	" " "	0.1825	0.1510	
	" " "	0.1756	0.1441	
P147	1753 / 1.2 PD / 11.3 Sel FB	0.1458	0.1143	$\bar{x} = 114.4 \text{ MG} \pm 0.36 (0.32\%)$
	" " "	0.1456	0.1141	
	" " "	0.1463	0.1148	

* 1.0 mil PET 0.0315g on P69 this notebook

To Page No. 1

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Date